a. a high density lipoprotein in contact with leukocytes of said sample of fresh blood;

b. about 0.1 to about 2 parts by weight of an agent for lysing erythrocytes in a sample of fresh blood for permitting cytometric analysis of said leukocytes; and

c. up to about 5 parts by weight of a preservative selected from the group consisting of diazolidinyl urea (DU), imidazolidinyl urea (IDU), an oxazolidine and mixtures thereof.

40. (Once Amended) A reagent composition for flow cytometric analysis of a sample of fresh human blood, comprising:

a. about 0.01 to about 5 parts by weight of a high density lipoprotein in contact with leukocytes of said sample of fresh human blood for minimizing lysis of said leukocytes;

b. an agent for lysing erythrocytes in a sample of fresh blood for permitting cytometric analysis of said leukocytes; and

c. up to about 5 parts by weight of diazolidinyl urea (DU).

42 ~~41~~. (New) A reagent composition for flow cytometric analysis of a sample of fresh human blood, comprising:

a. a high density lipoprotein in contact with leukocytes of said sample of fresh human blood; and

b. diazolidinyl urea (DU) in contact with leukocytes of said sample of fresh human blood.

Remarks

In the Office Action mailed September 14, 2001 and made final, the Examiner rejected claims 1,5,9-11 and 35-40 under 35 U.S.C. 103 as allegedly unpatentable over Young et al (Pat. No. 5,529,933) in view of Ryan (Pat. No. 5,460,797).

The undersigned thanks the Examiner for the courtesies extended in a personal interview on February 11, 2002. At the interview, the pending claims and rejections were discussed. Also discussed were proposed amendments

(namely, to present all claims as composition claims)[1] that would obviate the Examiner's objections set forth in the Action of January 15, 2002. Accordingly, in view of the focusing of issues at the interview, Applicants hereby submit the present Amendment, intended as a substitute for Applicants' December 12, 2001 Amendment Accompanying Request for Continued Examination.

The present pending claims have been amended according to the discussions at the interview. Basis for the amendments can be found, without limitation, at page 2, line 27, page 4 line 23 et seq, page 7, lines 4 et seq, page 7, lines 30-35, the Examples and claim 4 as filed, all of which address flow cytometric analysis of fresh human blood.

In view of the amendments and the following remarks the claims are believed patentable and favorable consideration is respectfully requested. Specifically, the nature of the amendments are to point out that the present composition is a reagent for contacting fresh blood in the course of conducting a flow cytometric analysis of the blood, such as for phenotyping blood cells or otherwise. Applicants also have incorporated relative proportions of the ingredients. Young certainly fails to teach provide any motivation for the selection of such proportions, in a single mixture[2], especially in combination with all of the recited components (certain of which the Examiner acknowledges are absent from Young). As was discussed at the interview the Young patent is directed to compositions for providing hematological reference controls. The different ingredients of the present claims invention are not believed to be taught or suggested in the combination recited, nor in the proportions recited by Applicants.

Further Young does not appear to teach or suggest the function performed by the lipoprotein disclosed for minimizing lysis (when employed in

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[1] As discussed at the Interview, Applicants have presented amended claims by referring to the composition as it would be present in its intended use. All of the claims have been amended to specifically contemplate that leukocytes from a human patient blood sample (in contrast with a reference control material), to be analyzed by flow cytometry, are contacted with lipoprotein.

[2] Young does not appear to provide any teaching of a mixture of both a lysing agent and a lipoprotein for treating a sample of fresh human whole blood. At best, Young arguably discloses treatment of cells with a lipoprotein followed by contact of the cells with a lysing agent. The discussion, however, is generally in the context of preparing leukocyte blood cell analogs by suspending washed red blood cells from a non-human source (e.g., goose or alligator cells; see col. 12, lines 52-55; and col. 8, lines 11-21).

a composition having a lysing agent) of said leukocytes in the preparation of cells for analysis, such as phenotyping or otherwise, by a flow cytometer.

Young is directed mainly at controls for hematological instruments that count cells. Young does not appreciate the claimed combination, particularly to perform flow cytometric analysis for analyzing the presence of human surface antigens on leukocytes of fresh human blood from a patient, an advantage made possible by the use of Applicants' composition.

Rather, Young teaches that its cells (which are not sample human cells) that are analyzed by a flow cytometer, but rather are animal cells that are stabilized (e.g. with an aldehyde, the potential toxicity of which typically compels particular handling requirements) for long term stability, for mimicking human WBC to a counting instrument.

As mentioned above, Applicants also believe that Young does not teach or suggest the simultaneous presence of each of the recited ingredients in applicants' claims especially in the presence of fresh human blood in a flow cytometer.

The Ryan patent relied upon by the Examiner is not properly combined to arrive at the claimed invention. The specification of Ryan does not address the presence of lipoprotein.[3] Accordingly, the present claimed combination is also patentably distinct over Ryan.

In short, the presently claimed combination is patentable over the art of record. Reconsideration and withdrawal of the present rejection is respectfully requested at the earliest convenience.

Notification of Patent Issue

Applicants also notify the Examiner that U.S. Application Serial No. 09/500,248, of record in the present application, has issued as U.S. Patent No. 6,357,189.

[3] By no means is this a concession that the presence of a lipoprotein would avoid the claims of Ryan. Indeed, thought not recited as a claim element, the Ryan claims could cover certain compositions that include lipoprotein, particularly in view of the transition "comprising".

Conclusions

In view of Applicants' amendments and remarks, the Examiner's rejections are believed to be rendered moot. Accordingly, Applicants submit that the present application is in condition for allowance and requests that the Examiner pass the case to issue at the earliest convenience. Should the Examiner have any question or wish to further discuss this application, Applicant requests that the Examiner contact the undersigned at (248) 593-9900.

If for some reason Applicants have not requested a sufficient extension and/or have not paid a sufficient fee for this response and/or for the extension necessary to prevent the abandonment of this application, please consider this as a request for an extension for the required time period and/or authorization to charge our Deposit Account No. 50-1097 for any fee which may be due.

Respectfully submitted,

Dated: Feb. 14, 2002

Eric M. Dobrusin
Registration No. 33,867
DOBRUSIN & THENNISCH PC
401 S. Old Woodward Ave., Ste. 311
Birmingham, MI 48009
(248) 593-9900

Customer No. 25215

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Twice Amended)A reagent composition for [preparing leukocytes for] flow cytometric analysis of a sample of fresh human blood, comprising:

a. a lipoprotein in contact with leukocytes of said sample of fresh human blood for minimizing lysis of said leukocytes;

b. an agent for lysing erythrocytes from said [a] sample of fresh blood for permitting flow [cytometric] analysis of said leukocytes; and

c. a preservative selected from the group consisting of diazolidinyl urea (DU), imidazolidinyl urea (IDU), an oxazolidine and mixtures thereof.

39. (Once Amended) A reagent composition for [preparing leukocytes for] cytometric analysis of a sample of fresh human blood, comprising:

a. a high density lipoprotein in contact with leukocytes of said sample of fresh blood;

b. about 0.1 to about 2 parts by weight of an agent for lysing erythrocytes in a sample of fresh blood for permitting cytometric analysis of said leukocytes; and

c. up to about 5 parts by weight of a preservative selected from the group consisting of diazolidinyl urea (DU), imidazolidinyl urea (IDU), an oxazolidine and mixtures thereof.

40. (Once Amended) A reagent composition for [preparing leukocytes for] flow cytometric analysis of a sample of fresh human blood, comprising:

a. about 0.01 to about 5 parts by weight of a high density lipoprotein in contact with leukocytes of said sample of fresh human blood for minimizing lysis of said leukocytes;

b. an agent for lysing erythrocytes in a sample of fresh blood for permitting cytometric analysis of said leukocytes; and

c. up to about 5 parts by weight of diazolidinyl urea (DU).

41. (New) A reagent composition for flow cytometric analysis of a sample of fresh human blood, comprising:

a. a high density lipoprotein in contact with leukocytes of said sample of fresh human blood; and

b. diazolidinyl urea (DU) in contact with leukocytes of said sample of fresh human blood.